Inhalational Anaesthetics

HISTORY

• ***diethyl ether*** first used by William T.G. Morton in the USA in 1846
• ether survived as a viable agent for many years because it,

a. is readily made in pure form
b. is a volatile liquid, therefore easily vaporised
c. is potent, only a few volumes % required, averting hypoxia
d. supported respiration and the circulation

• ***chloroform*** was the next agent to receive attention, by James Simpson in 1847
• apart from its pleasant odour and nonflammability, it had major problems,

a. severe cardiovascular depression (sudden death ? VF)
b. dose dependent hepatotoxicity

• ***cyclopropane*** was discovered accidentally in 1929 and was very popular for almost 30 yrs
• however, the increasing use of electronic equipment necessitated the production of a nonflammable agent

• a variety of other agents were investigated but discarded for various reasons,

a.	***explosive*** mixtures with oxygen	- diethyl ether - ethyl chloride - divinyl ether - cyclopropane
b.	postoperative liver necrosis / sudden death	- chloroform
c.	postoperative renal failure	- methoxyflurane

• ***halothane***, developed by ICI, was introduced in 1956 and revolutionised anaesthetic practice
• this recently has come in to some disrepute for postoperative liver failure
• ***enflurane*** has been in use since 1970
• difficulties with purification and suspected cardiotoxicity delayed the introduction of its isomer, ***isoflurane***, until recently (1981)

• ***desflurane*** is expected to be released for use in Australia, possibly by 1996
• this will provide an agent with the kinetics of cyclopropane without the flammability

MINIMUM ALVEOLAR CONCENTRATION

Def'n: the minimum alveolar concentration of anaesthetic, at ***equilibrium***, at ***one atmosphere*** pressure, which produces immobility in **50%** of subjects exposed to a standard noxious stimulus, which, for humans is surgical incision of the skin

- the rationale for this measure of anaesthetic potency is,
  a. alveolar concentration can be easily measured
  b. near equilibrium, alveolar and brain tensions are virtually equal
  c. the high cerebral blood flow produces rapid equilibration

- factors which support the use of this measure are,
  a. MAC is invariant with a variety of noxious stimuli
  b. individual variability is small
  c. sex, height, weight & anaesthetic duration ***do not*** alter MAC
  d. doses of anaesthetics in MAC's are additive

- for a number of anaesthetic gases, 1.3 MAC ~ 21 mmol/l in brain lipids
- the slopes of the dose/response curves are steep
- although only 50% of subjects do not respond at 1 MAC, 99% are unresponsive at ***1.3 MAC***
- another measure is the ED_{50}, which for the common inhalational agents is ~ MAC + 20%
- this is a less accurate measure as it does not refer to the alveolar concentration, which for a given inhalational dose will vary with agent solubility and patient uptake
- all the inhalational agents have a low margin of safety, with therapeutic indices of 2 to 4

NB: MAC represents only a single point on the dose response curve for the production of anaesthesia;
other effects, such as cardiovascular depression, may not be proportional

Factors Which Affect MAC

- ***Increase MAC***

  i. hyperthermia
  ii. hypernatraemia
  iii. drug induced elevation of CNS catecholamine stores
  iv. chronic alcohol abuse ? chronic opioid abuse (MCQ)
  v. increases in ambient pressure (experimental)

- ***Decrease MAC***

i.	hypothermia	- halothane $MAC_{27°C}$ ~ 50% $MAC_{37°C}$ - decrease is ~ linear
ii.	hyponatraemia	
iii.	increasing age	- MAC_{Hal} < 3 mths ~ 1.1 % - MAC_{Hal} > 60 yrs ~ 0.64 %
iv.	hypoxaemia	- $P_{aO2} \leq 40$ mmHg
v.	hypotension	
vi.	anaemia	
vii.	pregnancy	? progesterone
viii.	CNS depressant drugs	- opioids - benzodiazepines - major tranquilizers - TCA's
ix.	other drugs	- lithium - lignocaine - magnesium - pancuronium (?)
x.	acute alcohol abuse	

- ***No Change in MAC***

  i. sex
  ii. weight, BSA
  iii. type of supramaximal stimulus
  iv. duration of anaesthesia
  v. hypo/hyperkalaemia
  vi. hypo/hyperthyroidism
  vii. P_{aCO2} ~ 15-95 mmHg
  viii. P_{O2} > 40 mmHg
  ix. MAP > 40 mmHg

MOLECULAR ACTION OF INHALATIONAL ANAESTHETICS

Interruption of Neuronal Transmission

NB: there is ***no*** experimental data to support an action of the inhaled agents at specialised peripheral ***receptors***,
there is good evidence for ***differential sensitivity*** of various neuronal groups to the action of the inhaled agents,

this would be in keeping with a ***membrane site*** of action (see later)

• postsynaptic potentials are depressed to a proportionately ***greater*** extent than fibre compound action potentials
• depending upon the fibre group, the former may be almost totally abolished in the absence of any significant effect on axonal AP's
• axons may actually show a biphasic response, with initial enhanced excitability, followed by depression
• although axonal transmission appears affected to a lesser extent, this may still be significant in terms of transmitter release and the effects upon synaptic transmission may be, in part, due to this

• the following factors also influence susceptibility,

a. fibre diameter — $MAC_{fibre} \propto 1/\sim diameter$
b. stimulation frequency — $MAC_{fibre} \propto 1/freq.\ Hz$
c. axonal region — branch pts. > axons

• the action of the inhaled agents on ***synaptic transmission*** may be due to alteration of either,

a. presynaptic transmitter release
b. reuptake of transmitter following release
c. binding to post/pre-synaptic receptor sites
d. membrane conductance following receptor activation

• in contrast to what might be expected from the above, polysynaptic pathways are ***not*** depressed to a greater extent than monosynaptic pathways
• the inhaled agents appear to ***equally*** depress ***monosynaptic*** and ***polysynaptic*** responses recorded from the ventral root of the spinal cord (Miller)

■ *Alterations of Neuroregulators with Anaesthesia*

• in addition to the "classical" neurotransmitters, there is an ever-growing list of endogenous peptides, amino-acids, etc., which modulate neuronal transmission
• further, the postsynaptic action potential results in the formation of second mesengers which further mediate changes in neuronal transmission

• ***acetylcholine*** levels are not affected by any of the volatile agents, however, there is a decrease in the turnover rate
• synthesis is impaired by N_2O 70% or halothane 3%

• levels of ***catecholamines*** are similarly unaffected, however drugs which alter the availability of NA significantly alter anaesthetic requirement
• in contrast, CNS levels of ***dopamine*** appear to be inversely related to anaesthetic requirement
• administration of levodopa produces a dose-dependent reduction of MAC_H in rats
• the administration of α_2-adrenergic agonists markedly reduces MAC
• ***clonidine*** reduces the MAC_H in dogs by up to 42%
• ***d-medetomidine***, a more selective α_2-agonist, produces a MAC_H reduction in dogs to ~ 10% of the control value
• this is supposedly due to presynaptic inhibition of NA release, in addition to postsynaptic depression of neuronal excitability

• ***serotonin*** levels are unaltered generally, though, may increase in specific regions

→ substantia nigra & dorsal raphe nucleus

• ***gabba-aminobutyric-acid*** metabolism is depressed and content increases with halothane 3%
• however, uptake and release are unaffected, and the significance of the accumulation of GABA in inhibitory neurones is uncertain
• most studies demonstrate an increase in CNS ***cyclic AMP***
• this results from a reciprocal activation of adenylate cyclase and inhibition of phosphodiesterase
• levels of cGMP are reduced by the volatile agents
• these may, via phosphorylation, alter macromolecules involved in neuronal transport

• it was hypothesised in the late 1970's that the volatile agents acted via the ***opiate receptors***
• supporting this was the reduction in MAC with the use of opiates and the partial reversal of volatile agent action with the administration of ***naloxone***
• this later event more likely represents a general increased CNS excitation, rather than competition for the opiate receptor
• another mechanism for this hypothesis was that volatile agents acted via release of endogenous opioids within the CNS
• there is some animal data to support this, however there is no elevation of opioid peptides in the CSF of human subjects anaesthetised with volatile agents

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NB: in summary, the predominant effects of the volatile agents ***cannot*** at present be explained by depletion, production, or release of a single neurotransmitter

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Theories of Anaesthetic Action

1. Lipid Solubility - Overton & Meyer
2. Alterations to Lipid Bilayers
   - i. lipid perturbation - dimensional change
   - ii. lipid phase transition - "lateral phase separation"
   - iii. lipid-protein interactions
3. Alteration to Protein Function - luciferase inhibition

▪ *The Physicochemical Basis of Anaesthetic Action*

• a myriad of molecular species can produce general anaesthesia, including inert gases, simple inorganic and organic molecules, haloalkanes, and ethers
• the simple additive action of the anaesthetic agents suggests a nonspecific role, ie. their action is likely to be a ***physical process***, not a drug receptor interaction

NB: the idea that all anaesthetics have a common mode of action on a specific molecular structure, is called the ***unitary theory of narcosis***

• the best correlation with anaesthetic potency was noted to be the ***olive oil:gas partition coefficient*** by Meyer and Overton, 1899-1901
• the ***product*** of the anaesthetising partial pressure and the oil:gas partition coefficient varies little over ~ a 100,000 fold range of anaesthetising partial pressures
• this is species dependent, and in humans is,

$$P_{Gas} \times \tau_{O:G} \sim 1.28 \pm 0.09 \text{ bar}$$

• the amazing closeness of this relationship supports a unitary molecular site of action and suggests that anaesthesia results when a ***critical number*** of anaesthetic molecules occupy a crucial hydrophobic region in the CNS
• this relationship has led a search for the molecular basis in cellular hydrophobic regions

• the Meyer-Overton rule postulates that it is the ***number*** of molecules which are present at the site of action which is important and not their type
• thus, this hypothesis supports the ***additive*** nature of anaesthetic agents

Exceptions to the Meyer-Overton Rule

• enflurane and isoflurane are structural isomers and have similar oil:gas partition coefficients, however, the MAC for isoflurane is only ~ 70% of that for enflurane
• thus, it would appear that there are other factors which influence potency, these include,

1. ***convulsant properties***
   - complete halogenation, or complete end-methyl halogenation on alkanes & ethers results in decreased anaesthetic potency and the appearance of convulsant activity
2. ***the "cutoff effect"***
   - increasing homologues of ***alkane*** series a display cutoff point, beyond which anaesthetic potency sharply decreases
   - one postulate is that the larger members of a series are to large to fit into the "anaesthetic site"
3. ***specific receptors***
   - for a given MAC reduction, plasma levels of morphine, alfentanyl, sufentanyl, and fentanyl vary ~ 5000 fold
   - levels of these four agents in brain lipid vary ≤ 10 fold
   - thus, studies of the reduction in MAC by opioids suggests two sites of action,
   i. the opioid receptor
   ii. some hydrophobic site
   - d-medetomidine, an α_2-agonist results in a marked reduction in MAC, whereas its optical isomer, with identical lipid solubility has no effect

Hydrophillic Site Of Action

• L. Pauling & S. Miller (1961) independently proposed that anaesthesia may result from the formation of ***clatharates of water*** in membranes
• anaesthetic molecules acting as seeds for crystals of water which subsequently alter membrane ion transport
• this is less likely than the unitary theory, as there is a poor correlation between the ability of agents to form clatharates and their anaesthetic potency

• Traube (1904) and Clements & Wilson (1962) proposed that potency correlated with reduction of ***surface tension***
• however, these later physical properties are closely related to those physical properties which determine ***hydrophobicity***

Critical Volume Hypothesis

• although the Meyer-Overton rule postulates that anaesthesia results when a certain number of molecules dissolve at a certain site, it does not explain why anaesthesia results
• as anaesthetic action displays ***pressure reversal***, Mullins (1954) proposed that anaesthetic potency should correlate directly with both ***lipid solubility*** and ***molar volume***
• anaesthesia occurring when the volume of the hydrophobic region is caused to expand beyond some ***critical volume***
• this theory is supported by a number of experimental observations,

a. hydrostatic pressure reversal
b. volume expansion of model lipid membranes
c. He & Ne, low lipid solubility gases are not anaesthetics[§]
d. the potency of hydrogen << predicted[§]

NB: [§]that is, the volume expansion caused by these agents is ***offset*** by the compression resulting from the high hydrostatic pressures required

• arguments against this hypothesis include,

a. decreasing temperature should decrease relative volume expansion and ***increase*** MAC requirement
b. that not all lipid soluble agents are anaesthetics
c. the non-linear pressure antagonism for certain agents

Anaesthetic Binding to Membrane Lipids

• biological membranes consist of a cholesterol-phospholipid bilayer, having a thickness of ~ 4 nm
• peripheral proteins are weakly bound to the exterior hydrophilic membrane
• integral proteins are deeply imbedded in, or pass through the lipid bilayer
• synaptic membranes are ~ 50:50 lipid bilayer & protein by weight
• the correlation of potency and solubility of anaesthetic agents in phospholipid bilayers is at least as good as that for olive oil

Effects on Membrane Permeability

• examining ion fluxes across synthetic liposomes, all inhalational agents increase ***cation flux***
• the magnitude of the increase depends upon lipid composition and the agent examined
• these increases in cation flux are reversed by high pressures (~ 100 Atm)
• these effects are also seen with lipid vesicles, and it has been postulated that the reduction in the normal transvesicular pH gradient results in inability of the vesicles to retain catecholamines
• this leads to intraneuronal depletion of catechol stores and reduced transmission
• experimental depletion, however, can only reduce MAC ~ 40% and this can only be a contributing factor

Effects on Membrane Dimension

• the absorption of anaesthetic into lipid monolayers increases lateral pressure
• theoretically this may affect ion channel function
• this effect parallels anaesthetic potency and is a variation of the volume expansion theory
• however, the measured increases in volume of prepared monolayers are only small and may be due to other factors,

a. increased hydration in the bilayer
b. altered lipid water interactions
c. conformational changes in the lipid phase

Alteration of Membrane Physical State

• phospholipid membranes undergo a transition with increasing temperature, called the ***gel-liquid crystalline transition*** of the lipid matrix
• this transition is associated with an increase in the ***molar volume*** of the lipid
• Trudell *et al*. (1973) showed that in the presence of anaesthetic agents this transition occurs at a lower temperature, and over a wider temperature range
• even small changes in fluidity of the membrane (~ 1-2%) result in increased cation flux across liposomes
• lipids surrounding ion channels are held in the more rigid gel state, dissolution of which allows channel closure
• incompatible with this idea, is the fact that hypothermia decreases fluidity but enhances anaesthetic action

• an alternative proposal, is the "lateral phase separation hypothesis"
• using NMR and ESR techniques, these agents cause a local disordering of the phospholipid matrix and reduce the number of molecules which simultaneously alternate between the gel & liquid crystalline states
• reducing such fluctuations, these agents thereby reduce the magnitude of fluctuations in volume which probably occur in dynamic biological membranes
• such volume fluctuations allowing channel conformational change

• both the ***fluidization*** and ***lateral phase separation hypotheses*** suggest that anaesthesia results from making the membrane more disorganised, or fluid
• this would then be reversible by the application of high pressure
• these theories are compromised by,

a. small increases in temperature (~ 1°C), result in the same degree of fluidization as clinical concentrations of inhalational agents and therefore should augment anaesthesia
b. increasing age is accompanied by the progressive accumulation of rigidifying lipids, which should oppose this action

Alteration of Protein Function

NB: most investigators agree that the final common action of inhaled anaesthetic agents is on specific neuronal membrane proteins involved in ion fluxes

Soluble Proteins

• distinct anaesthetic binding sites have been found in a number of proteins,

i. haemoglobin
ii. myoglobin
iii. serum albumin

• this binding is readily reversible, and appears to result in virtually no significant alteration in protein function for most plasma enzymes
• other proteins are quite sensitive to anaesthetic binding
• the bacterial enzyme ***luciferase*** is readily inhibited at ≤ 1 MAC
• the "cutoff effect" can be demonstrated with a purified firefly luciferase preparation
• this effect may extrapolated in theory to enzymes involved in neuronal excitability

Membrane Proteins

• there are two major problems with trying to study membrane bound protein function,

a. isolation of significant numbers is difficult and time consuming
b. proteins then need to be re-incorporated into a lipid membrane to study their function

• clearly it is difficult to distinguish between effects on the surrounding membrane lipid and distinct effect on the proteins themselves
• the ***ACh-receptor/ionophore*** complex is the best characterised with regard to anaesthetic influence
• volatile agents stabilise the receptor in a state which forms high affinity bonds with agonist molecules, thus producing a desensitised and closed channel state
• although there is a fair correlation between anaesthetic potency and increased binding affinity, minimal desensitisation occurs at clinical concentration
• also, very high concentrations actually decrease ACh binding, thus there is no linear dose-response relationship
• interaction with ***rhodopsin*** has also been examined but effects are only seen at very high concentrations
• recent work suggests that membrane ***G-proteins*** may be a site where significant alteration of membrane function occurs
• these are inhibited by pertussis toxin and intracerebroventricular injection of pertussis toxin increases halothane MAC ≥ 70%
• the reduction in halothane MAC seen with α_2-agonists is also attenuated by pertussis toxin

NB: in summary, there are a number of possible sites where anaesthetics may have a significant action, however, good experimental evidence is still wanting

UPTAKE AND DISTRIBUTION OF INHALATIONAL AGENTS

NB: the depth of anaesthesia varies directly with the ***tension*** of the agent in the brain, and, therefore, the rates of induction and emergence depend upon the rate of change of gas tension in the blood and tissues

- the alveolar partial pressure is in equilibrium with arterial blood and therefore brain tissue
- thus, alveolar concentration is an indirect measure of brain concentration
- the factors which determine this may be considered as acting in separate stages,

1. Transfer from ***Inspired Air to Alveoli***

i.	the inspired gas concentration	F_I
ii.	alveolar ventilation	V_A
iii.	characteristics of the anaesthetic circuit	

2. Transfer from ***Alveoli to Arterial Blood***

i.	blood:gas partition coefficient	$\tau_{B:G}$
ii.	cardiac output	CO
iii.	alveoli to venous pressure difference	$\delta P_{A\text{-}vGas}$

3. Transfer from ***Arterial Blood to Tissues***

i.	tissue:blood partition coefficient	$\tau_{T:B}$
ii.	tissue blood flow	
iii.	arterial to tissue pressure difference	$\delta P_{a\text{-}tGas}$

Transfer from Inspired Air to Alveoli

▪ *Inspired Gas Concentration*

• according to Dalton's law of partial pressures, the tension of an individual gas in inspired air is equal to,

$$P_{Igas} = F_{Igas} \times Atm$$

• the greater the inspired pressure the greater the approach of F_A to F_I = ***the concentration effect***
• this is only significant where F_I is ***very high***, as is the case for N_2O (or cyclopropane)
• when another gas is used in the presence of such an agent, there is increased uptake of the second gas, the ***second gas effect***
• the tension in the inspired gas is frequently limited by agent-induced airways irritability
• this can be attenuated partially by adequate premedication
• in practice, the inspired concentration is rarely constant
• irritating agent concentrations are slowly increased, c.f. agents where rapid induction can be achieved with "loading doses"
• this is why halothane, which should theoretically take longer to induce patients, is more rapid than the more irritant isoflurane
• when a constant tension is inhaled, the tension in arterial blood progressively approaches the tension in alveolar air (see G&G fig. 13-1)
• the rate at which this occurs is determined by the physical properties of the agent, see below
• however, during maintenance, F_I may be considerably greater than F_A, depending on the solubility of the agent

▪ *Alveolar Ventilation*

• each inspiration delivers some anaesthetic to the lung and, if unopposed by uptake into the blood, normal ventilation would increase F_A/F_I to 95-98% in 2 minutes
• this rate of rise is dependent upon ***minute ventilation*** and ***FRC***
• the greater the FRC, the slower the rise in F_A
• therefore, if minute ventilation is increased, the tension in alveolar air and arterial blood will rise more quickly → ***lung washin***
• the effects of the rate of respiration, to speed or slow induction, are transient for gasses such as N_2O which are poorly soluble in blood, and thus equilibrate quickly
• however, the minute volume of ventilation has a significant effect on the ***highly soluble*** agents, such as methoxyflurane or diethyl-ether
• hyperventilation will decrease CBF, and this tends to offset the increased rise of F_A/F_I

▪ *Anaesthetic Circuit* *(See Later)*

• three factors are important,

1. the volume of the external breathing system
2. the solubility of the given agent in the rubber and plastic components of the system
3. the gas inflow from the anaesthetic machine

Transfer from Alveoli to Arterial Blood

• the alveolar membrane poses no barrier to the transfer of anaesthetic gasses in either direction
• V/Q mismatch, by effectively increasing ***shunt flow***, will decrease the rate of transfer into blood, especially for agents of ***low solubility***
• in the absence of V/Q inequality, the product of three factors determines the speed of uptake,

$$\dot{Q}_{Gas} = \tau_{B:G} \times CO \times \frac{P_{A-vGas}}{P_{Atm}}$$

• where P_{Atm} is the barometric pressure
• should any of these components $\rightarrow 0$, then uptake will $\rightarrow 0$

▪ ***Blood:Gas Partition Coefficient***

• the solubility of a gas in liquid is given by its ***Ostwald solubility coefficient***, τ
• this represents the ratio of the concentration in blood to the concentration in the gas phase (c.f. Bunsen at s.t.p.)
• this is independent of ***pressure***, obeying Henry's law
• serum proteins and RBC's are the major determinants of solubility
• ***lower*** B:G coefficients are seen with,

i. haemodilution ~ 20% less when the Hct. = 21% c.f 43%
ii. obesity
iii. hypoalbuminaemia and starvation

• ***higher*** coefficients are seen in,

i. adults versus children
ii. hypothermia
iii. postprandially

• the more soluble an anaesthetic in blood, the more of it which must be dissolved to raise the partial pressure
• stated another way, soluble agents have a larger blood reservoir, the reservoir for insoluble agents is small and fills more quickly

NB: this is the principal determinant of the approach of F_A to F_I

Anaesthetic Agent	Blood:Gas coefficient at 37°C
Methoxyflurane	15
Halothane	2.4
Enflurane	1.8
Isoflurane	1.4
Sevoflurane	0.69
Desflurane (I-653)	0.42
Nitrous Oxide	0.47

- ***Cardiac Output CO***

• effectively pulmonary blood flow and determines the rate at which agents pass from gas to blood
• an increase in flow will slow the initial portion of the arterial tension/time curve by delaying the approach of F_A to F_I
• a low CO state, conversely, will speed the rise of F_A/F_I
• these effects are greater for ***highly soluble*** agents

NB: thus, anaesthetic induced CVS depression may cause a more rapid rise in arterial tension (Eger 1986)

- ***Shunt***

• an increase in shunt flow has two effects,

1. increased $P_{A.Gas}$ - small for insoluble agents
   - moderate for soluble agents
2. decreased $P_{a.Gas}$ - very large for ***insoluble*** agents
   - negligible for soluble agents

NB: $\rightarrow$ a large $\delta P_{A\text{-}a.Gas}$ gradient develops for ***insoluble*** agents

• this effectively slows the induction of anaesthesia in the presence of significant shunt, eg. endobronchial intubation, CHD

- ***Alveoli to Venous Pressure Difference***

• this represents ***tissue uptake*** of the inhaled agent
• blood cannot approach equilibrium with alveolar air until the distribution of anaesthetic from the blood to the tissues is nearly complete
• with equilibration, the alveolar/mixed venous tension difference progressively falls as tissue tensions rise
• since diffusion is directly proportional to the tension difference, the rate of diffusion into the blood progressively slows

Transfer from Arterial Blood to Brain & Tissues

- the rate at which gas passes into the tissues depends on,
    i. tissue:blood partition coefficient
    ii. tissue blood flow
    iii. arterial to tissue pressure difference, $\delta P_{a\text{-}t.Gas}$

▪ *Tissue:Blood Partition Coefficient*

- for most anaesthetic gasses, this is near unity for ***lean tissues***
- the rate of rise of tension in these regions is proportional to the arterial-tissue tension difference
- conversely, their solubility in ***lipid tissues*** is far greater than that for blood
- at equilibrium the concentration in lipid tissues will be far greater than that in blood
- the tissue concentration will rise above that of blood well before pressure equilibrium, even though the tissue tension is lower

Anaesthetic Agent	Fat:Blood coefficient at 37°C
Methoxyflurane	61
Halothane	62
Enflurane	36
Isoflurane	52
Sevoflurane	55
Desflurane (I-653)	30
Nitrous Oxide	2.3

▪ *Tissue Blood Flow*

- the higher the blood flow to a region, the faster the delivery of anaesthetic and the more rapid will be equilibration
- the total amount of gas dissolved will, however, depend upon the tissue volume and agent solubility in that tissue
- the body tissues have been divided into groups according to their level of perfusion and tissue blood flow,

a.	vessel rich group	**VRG**	- brain, heart, kidney & liver
b.	the muscle group	**MG**	- muscle & skin
c.	the fat group	**FG**	- large capacity/minimal flow
d.	vessel poor group	VPG	- bone, cartilage & CT

Tissue Compartment Kinetics[1]				
Group	Blood Flow % CO	Body Mass	Flow (l/hr)	Equilibration time[2]
VRG	75	< 10%	45	3-10 min
MG	18-20	45-50%	2	1-4 hrs
FG	5	15-20%	1.3	≤ 5 days
VPG	no pharmacokinetic significance (Eger 1974)			

[1] from Dale et al., Clinical Pharmacokinetics (12:145-167,1987)

[2] these variations are more important for the ***highly soluble***, in this case tissue soluble agents

- ***Arterial-Tissue Pressure Difference***

• with equilibration tissue tension rises and the rate of diffusion slows, as does uptake in the lung
• the rate is determined by the tissue ***time constant***, which in turn depends upon both the tissue ***capacity*** ($\tau_{T:B}$) and the tissue ***blood flow***

$$TC(\tau) = \frac{Tissue\ Capacity/100g}{Blood\ Flow/100g}$$

NB: as for any ***exponential process***, 3 time constants $\rightarrow$ 95% equilibrium point

Brain Compartment Time Constants			
Anaesthetic Agent	$\tau_{brain:blood}$ (37°C)	TC (min)	Equilibrium
Methoxyflurane	2	3.6	11
Halothane	2.6	4.7	14
Enflurane	2.6	4.7	14
Isoflurane	3.7	6.7	20
Sevoflurane	1.7	3.1	9.3
Desflurane (I-653)	1.3	2.4	7.1
Nitrous Oxide	1.1	2	6

NB: thus, as the VRG receives 75% of the CO, after 3 time constants, 75% of the returning venous blood will be in equilibrium with P_{AGas}

Other Factors Affecting Uptake & Distribution

- ***Concentration and Second Gas Effects***

  Def'n: the ***concentration effect*** states that with higher inspired concentrations of an anaesthetic, the rate of rise in arterial tension is greater

• eg., during the inhalation of 75% N_2O/O_2, initially as much as 1 l/min may diffuse into the bloodstream across the lungs
• this effectively draws more gas into the lungs from the anaesthetic circuit, thereby increasing the ***effective minute ventilation***
• this effect is also important where there is a ***second gas***, such as 1% halothane, in the inspired mixture
• the removal of a large volume of N_2O from the alveolar air increases the delivery of the second gas, effectively increasing its delivery to the alveoli and increasing its diffusion into arterial blood

- ***Diffusion Hypoxia***

• first described by Fink in 1955
• this is effectively the reverse of the above
• the elimination of a poorly soluble gas, such as N_2O, from the alveoli may proceed at as greater rate as its uptake, thereby adding as much as 1 l/min to alveolar air
• this gas effectively dilutes alveolar air, and available oxygen, so that when room air is inspired hypoxia may result
• this is usually only mild and rarely clinically significant
• although this may occur with any anaesthetic agent, its magnitude is insignificant unless an insoluble agent, such as nitrous oxide, has been inhaled for some time
• under these circumstances as much as 30 l may be dissolved in the blood and tissues

- ***Alterations in Ventilation & Perfusion***

• previous discussion has assumed independent changes in either of these variables
• if both increase proportionately then the rate of rise of F_A/F_I might be expected to remain constant
• this would be the case, except for the greater delivery of agent to the tissues and the accelerated narrowing of $P_{A\text{-}vGas}$
• thus the rate of rise of F_A/F_I is increased
• the magnitude of this acceleration is dependent upon the distribution of the increase in CO
• where this increase is greater to the VRG, a far greater effect is seen
• this contributes to the faster induction of children, especially infants, & pregnant women

Elimination of Inhaled Anaesthetics

• the factors affecting the elimination of an anaesthetic agent are identical to those for uptake and distribution (see G&G fig. 13-2)
• these factors equally apply for changes in the depth of anaesthesia
• there are, however, two differences between uptake and elimination,

1. the augmentation of the rise of F_A/F_I by ***overpressure*** is not possible
2. on induction all tissue groups $P_{Gas} = 0$, whereas, these all vary with elimination

• due to the time constants for the tissue groups, neither the MG nor the FG have come to equilibrium at the end of a halothane anaesthetic
• consequently these groups, especially the FG, continue to take up agent and actually contribute to the decline of F_A/F_I during the first few hours
• the failure of several tissues to reach equilibrium has two effects,

1. recovery is ***more rapid*** than induction (without overpressure)
2. recovery is dependent upon the ***duration*** of anaesthesia

• the saturation of enzyme systems responsible for metabolism effectively reduces any impact this might have of the rate of rise of F_A/F_I during induction
• this limitation does not exist in recovery and results in a faster decline in F_A for halothane c.f. enflurane
• thus, hepatic metabolism ***is*** a significant factor for the elimination of halothane, especially at low, sub-anaesthetic alveolar concentrations

▪ ***Intertissue Diffusion***

• work done by Carpenter *et al*. (1986) studying washout during recovery from anaesthesia support a 5 compartment model
• the time constants of four of these are in keeping with exchange with lung, VRG, MG and FG
• the time constant of the fifth lay between the MG & FG's, being ~ 400 min
• Carpenter postulated that anaesthetics diffuse from well perfused tissues to adjacent poorly perfused tissues which have a high capacity for the agent
• eg. from heart to pericardial fat, kidneys to perinephric fat etc.

NB: this may account for as much as 1/3 of the agent taken up

Anaesthetic Circuitry

- the above discussion assumed that F_I equals the anaesthetic machine delivered concentration, F_M
- this would occur if a non-rebreathing circuit was used, however in practice F_I is determined by,

a. F_M
b. the washin characteristics of the circuit
c. losses from the circuit by dissolution
d. the effects of rebreathing

▪ *Circuit Washin*

- clearly this is determined by the fresh gas flow and the volume of the circuit
- an average circle with a volume of 7l, with a FGF = 6.0 l/min and ***no*** uptake from the circuit,

a. corrugated hoses and fittings ~ 3.0 l
b. bag ~ 2.0 l
c. CO_2 absorbers ~ 2.0 l

→ F_I/F_M will be ~ 1.0 at ***5-6 minutes***

- the higher the FGF, the faster the rate of washin

▪ *Circuit Losses*

- both rubber and plastic components of the system may remove agent and slow circuit washin
- this is a significant problem for methoxyflurane, less so for halothane or isoflurane, and virtually insignificant for N_2O or desflurane

- similarly uptake may occur into soda lime
- this is small unless the soda lime is dry, when appreciable amounts of agent may be absorbed
- both dry & wet soda lime will absorb appreciable amounts of ***sevoflurane***

Circuit Solubility Characteristics

Anaesthetic Agent	Polyethylene (hoses)	Rubber (bag)	PVC (ETT)
Methoxyflurane	118	742	-
Halothane	128	190	223
Enflurane	-	74	-
Isoflurane	58	49	114
Sevoflurane	31	29	68
Desflurane (I-653)	16	19	35
Nitrous Oxide	-	1.2	-

The Effect of Rebreathing

- as inspired gas is actually fresh gas + exhaled gas, F_I will be determined by,
    a. the amount gas rebreathed
    b. the uptake of gas by the lung $\rightarrow$ F_{ET}

- an increase in either uptake or rebreathing will lower the F_I of a highly soluble gas more than that for an insoluble gas
- this effect may be decreased by decreasing rebreathing
- high FGF rates allow predictability of F_I but are obviously wasteful and result in drier inspired air

▪ ***Circle Systems***

- ultimately the amount of anaesthetic required is dictated by ***patient response***, however, an initial estimate may be made from the "square root of time formula" from Severinghaus
- this requires that the ***first minute uptake*** be estimated,

$$U_1 = \tau_{B:G} \,.\, CO \,.\, (P_A/Atm)$$

- P_A/Atm is used as the venous gas concentration may be assumed to be zero and the ***desired alveolar concentration*** is used
- uptake at subsequent times is then given by the formula,

$$U_t = \frac{U_1}{\sqrt{t}}$$

- thus, for ***enflurane*** this becomes,

$$\begin{aligned} \mathbf{U_1} &= \tau_{B:G} \,.\, CO \,.\, P_A/Atm \\ &\sim 1.9 \,.\, 5{,}000 \,.\, 0.01 \\ &\sim 95 \text{ ml} \end{aligned}$$

- and subsequently, $U_4 \sim 47.5$ ml
  $U_{16} \sim 24$ ml
  $U_{25} \sim 19$ ml

- in practice these volumes vary considerably, being affected by body weight, percentage fat, surface area, hypothermia, hypovolaemia, increasing age etc.
- this all becomes academic with the monitoring of $F_{ET.Gas}$

THE MODERN INHALATIONAL ANAESTHETICS

NB: the ideal inhalational anaesthetic should have the following properties

a. rapid and pleasant ***induction*** and emergence from anaesthesia
b. rapid and easily identified changes in the ***depth*** of anaesthesia
c. adequate ***relaxation*** of skeletal muscles
d. a wide ***margin of safety***
e. the absence of ***toxic*** or other adverse effects at normal doses
f. high degree of ***specificity*** of action
g. technically easy to administer
h. useful for all ***age*** groups

Physical Properties

• halothane is a ***haloalkane***, whereas enflurane and isoflurane are ***methylethyl ethers***
• substitution of the hydrogen atoms with ***halogens***, especially fluorine, results in stable, nonflammable compounds
• increasing substitution on the ***alkanes*** $\rightarrow$

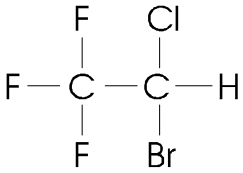
a. increasing anaesthetic potency
b. then convulsant activity, and
c. eventually an inert compound at full halogenation

• this process also increases the propensity to cause ***arrhythmias***

• the ***ethers***, conversely, are less prone to disturbances of cardiac rhythm
• all are potent anaesthetic agents, with low molecular weights and low boiling points
• they vaporise easily at room temperature from the liquid phase, and in clinical concentrations are nonflammable and nonexplosive

• ***halothane*** is chemically unstable, decomposing to HBr, HCl, and phosgene on exposure to light
• halothane is therefore supplied in amber coloured bottles requiring the addition of ***thymol 0.01%*** as a stabilising agent
• all have aromatic odours, isoflurane being the most pungent
• the relative oil:gas partition coefficients would suggest that induction and emergence should be most rapid with isoflurane > enflurane >> halothane
• toxicity is probably inversely related to chemical stability, and is thought to be caused by active products of biotransformation
• attempts have been made to increase the stability of these agents by ***deuterium***, ^{2}H, substitution

HALOTHANE

Structure:	
Chemical name:	2-bromo-2-chloro-1,1,1-trifluoroethane
Introduced:	1956 ICI
MAC:	0.75% 0.29% (70%-N_2O/O_2)
Partition Coefficient Bld-Gas: Oil-Gas: Fat-Bld:	 2.4 (2.3) 224 (330) 62
Saturated Vapour Pressure:	32% 243 mmHg (20°C)
Boiling Point:	50.2 °C
Molecular Weight:	197.4 g

Circulatory Effects

• as for most volatile anaesthetics, halothane possesses a narrow margin of safety, resulting in severe cardiovascular depression
• ***hypotension*** being the best indicator of anaesthetic depth, being dose-dependent
• halothane hypotension results from two factors,

a. direct myocardial depression - decreasing CO by 20-50%
b. obtundation of baroreceptor response - no reflex tachycardia

• early in halothane anaesthesia there is no decrease in TPR, though, this may fall and the HR rise with prolonged anaesthesia (≥ 5hrs)
• the order of potency for direct ***myocardial depression***, in decreasing order is,

Enflurane ≥ Halothane > Methoxyflurane > Isoflurane > Diethyl Ether

• these decreases in LV function are accompanied by increases in LVEDP
• cardiovascular depressive effects are exaggerated by β-antagonists
• however, recent studies show decreasing β-blockers prior to CABG surgery results in a greater incidence of new, perioperative ischaemic changes
• the predominant sites of action blocking the baroreceptor response are the effector sites in the heart controlling cardiac rate and/or contractility
• as with other volatile anaesthetics, there is no increased sympathoadrenal activity in response to cardiovascular depression

• however, at clinical depths of anaesthesia, the normal SNS response to surgical stimulation remains
• the reduction in CO is proportional to the tension of halothane and is enhanced by a reduced P_{aCO2}, evoking a decrease in SNS activity
• CVS responses to halothane are less exaggerated during spontaneous respiration, due to,

a. the elevated P_{aCO2} & increased SNS activity
b. the absence of the effects of IPPV on CO

• the decrease in myocardial contractility can be reversed by increasing [Ca^{++}] and, therefore, has been postulated to be due to a reduced availability of Ca^{++}

→ ? availability from SR, or decreasing $\boldsymbol{i}_{SI}$

• halothane is actually a nonspecific Ca^{++} influx inhibitor (Dale *et al.* 1987), and additive effects with verapamil should be expected (Eger 1984)
• the ***bradycardia*** seen with halothane is partially reversible with atropine, and is due to,

a. decreased cardiac sympathetic activity with ***vagal dominance***
b. direct slowing of the ***SA node***- decreased phase 4 depolarization
- increased threshold for depolarization*
c. enhanced vagal activity - airway manipulation

NB: → sinus bradycardia, wandering pacemaker, or junctional rhythms

these differ from the effects of ***ACh***, which does not alter the threshold V_m, but increases resting V_m and decreases phase 4 $\delta V/\delta t$

• ***tachyarrhythmias*** may also occur with halothane and tend to be of the reentrant type, due to,

a. slowing of ***conduction velocity*** (AV node & His-Purkinje)
b. increases the ***refractory period*** in conducting tissue

NB: → predisposition to ***reentry***,
ie., unidirectional block & slow retrograde conduction

• halothane increases the ***automaticity*** of the myocardium, and when combined with adrenergic agonists → ***ectopic pacemakers***
• such tachyarrhythmias are less likely to occur if,

a. anaesthesia is sufficient → decreased SNS stimulation
b. ventilation is adequate → CO_2 increasing SNS activity
c. use of ***adrenaline*** for haemostasis is limited
   i. concentrations < 1:100,000 = 1mg/100 ml
   ii. the total dose < 0.1 mg in 10 min = 10 ml
   < 0.3 mg in 1 hour = 30 ml

***1:200,000 ® 60 ml/hr, or 1 ml/min**

• ***coronary autoregulation*** remains intact and the decrease in coronary flow is due to the reduced myocardial oxygen consumption & work
• the following vascular beds do lose the ability to ***autoregulate***, with perfusion becoming proportional to MAP,

a. cerebral
b. renal
c. splancnic
d. pulmonary - loss of HPV $\rightarrow$ V/Q mismatch

NB: despite multiple vascular bed changes, ***TPR*** remains virtually constant, the decrease in arterial pressure resulting from decreased ***contractility***

Respiration

• halothane influences both the control of ventilation and the efficiency of pulmonary gas exchange
• it reduces tracheobronchial secretions, even without atropine
• the $P_{A\text{-}aO2}$ difference increases indicating an increase in shunt flow
• the ***shunt fraction*** during volatile anaesthesia routinely increases from 2-3% to ~ 10% in otherwise healthy individuals (Nunn)
• further, this increase in shunt occurs early during anaesthesia and is the same for SV & IPPV, despite the gross V/Q changes demonstrated by Froese & Bryan
• respiration characteristically becomes rapid and shallow, "diaphragmatic", with the following pattern,

a. minute volume is decreased
b. P_{aCO2} is increased - from 40 to ~ 50 mmHg
c. dose dependent decreased ventilatory response to CO_2 (and O_2)

• other effects of halothane anaesthesia and the origin of defects in pulmonary oxygen transfer include,

a. supine position altering regional lung blood flow
b. IPPV
c. altered lung volumes - esp. decreases in FRC
d. changes in relative movements of diaphragm and chest wall
e. bronchodilatation $\rightarrow$ increased V_D
f. depresses mucociliary flow
g. inhibition of hypoxic pulmonary vasoconstriction

NB: $\rightarrow$ effective increase in ***physiological shunt*** & ***dead space***

Nervous System

- EEG shows progressive replacement of fast/low voltage waves with slow waves of increasing amplitude
- surgical stimulation replaces this activity, c.f. normal ARAS arousal
- cerebral vessels dilate during halothane anaesthesia with loss of normal autoregulation

  $\rightarrow$ $\uparrow$ CBF & ICP

- this is of course unless there is excessive systemic ***hypotension***, further aggravating CPP
- CSF formation & reabsorption are both increased $\rightarrow$ minimal net effect
- cerebral MRO_2 falls and CBF is adequate for needs
- shivering during recovery is common and probably represents a response to heat loss and/or some ill-defined expression of neurological activity

Muscle

- there is some degree of muscle relaxation with halothane
- probably due to a central effect but also some increase in end-plate sensitivity to competitive blockers (?? effects of decreased blood flow)

> ***NB:*** the main effect is an increase in the duration and magnitude of blockade by competitive agents

- rarely associated with ***malignant hyperpyrexia***, characterised by,

  a. a rapid rise in body temperature

  b. a massive increase in MRO_2 and/or a low P_{aO2}

  c. an increased P_{aCO2} and marked acidosis

- this may occur due to failure of uptake of Ca^{++} into the SR in genetically susceptible individuals
- ***uterine*** smooth muscle is relaxed by halothane, possibly by an action on β-adrenergic receptors
- this may be useful in manual version of a foetus, however, predisposes to accentuated blood loss during parturition

Kidney

- doses of 1 MAC decrease RBF and GFR by up to 40-50%
- this may be greater if there is pre-existing hypovolaemia
- in normovolaemic subjects, halothane does not interfere markedly with autoregulation, or the cortical/medullary distribution of blood flow
- there is usually good recovery of function post-operatively
- occasionally may produce SIADH with H_2O retention and hyponatraemia
- this usually only occurs in the elderly

Liver and GIT

- intestinal, and therefore hepatic blood flow are reduced in proportion to perfusing pressure
- hepatic blood flow falls by ~ 25-30% with 1.5% inhaled halothane
- the liver shows decreased hepatocellular function and MFO activity with reduced drug clearance
- these effects are normally rapidly reversed on cessation of anaesthesia

Halothane Hepatotoxicity

- the first reports in appeared in **1958**
- subsequently investigated in the "National Halothane Study (1966)" but toxicity was not confirmed
- this is now accepted but convincing animal models still lacking
- most common causes of postoperative hepatic dysfunction are still ***viral hepatitis***, or damage by known ***hepatotoxins***
- rarely, one sees postoperative hepatitis, ~ **1:10,000** anaesthetics, where no other cause can be identified
- this usually occurs at 2-5 days postanaesthesia, and is characterised by,
    i. fever
    ii. N&V
    iii. a rash
    iv. an eosinophilic blood picture

- this may progress to fulminant hepatic failure, and of these ~ 50% die
- an increased incidence is found after repeated administration of halothane within a short time interval $\rightarrow$?? abnormal immune response
- biotransformation and the production of reactive intermediaries is another possible mechanism
- however, these are short-lived and bind close to their site of production, hence are very difficult to study
- ?? ***trifluoroacetyl*** intermediates bind to liver macromolecules which form a ***hapten*** and immunogenic liver damage results in susceptible individuals
- two animal models exist,

    a. rats, pretreated with phenobarbital and exposed to hypoxia
    ? reductive pathway & free F^- production (see below)

    b. rats, pretreated with polychlorobiphenyls + halothane 1% / O_2 99%
    $\rightarrow$ centrilobular hepatic necrosis

    NB: however, both of these are only animal studies and require considerable enzyme induction, or some other additional factor

Biotransformation

- 60-80% is exhaled unchanged within 24 hours
- **15%** is metabolised by liver MFO system
- however, this figure may vary and appears to be inversely proportional to the inspired concentration
- recent mass balance studies in humans → £ ***40-50%*** may be ***metabolised***
- initially pulmonary elimination predominates, however as the F_A falls a greater percentage is eliminated by hepatic metabolism

- halothane is metabolised by two routes,

a. ***oxidative*** → trifluoroacetic acid
Br^- & Cl^-
trifluoroacetic acid-ethanolamide conjugate

b. ***reductive*** → 2-chloro-1,1,1-trifluoroethane*
2-chloro-1,1-difluoroethylene*
Br^- & F^-

c. soda lime → 2-bromo-2-chloro-1,1-difluoroethylene*
?? conjugation with N-acetylcysteine via glutathione and urinary excretion

NB: * these metabolites are ***volatile***

- little F^- is removed due to the high C-F bond energy (~ 2x C-Cl or C-Br)
- blood ***bromine*** concentrations may contribute to postoperative somnolescence
- levels as high as 3.0 mmol/l have been recorded
- the [metabolites] peaks 24 hours after halothane anaesthesia, and these are eliminated by renal excretion over the following week
- halothane itself is a weak inducing agent, however halothane metabolism can be induced by phenobarbital, etc.
- the major urinary metabolite is ***trifluoroacetic acid***, which itself is not considered to be toxic
- however, its ***trifluoroacetyl intermediate*** may play a role in the liver toxicity of halothane
- prolonged exposure → ? increased incidence of miscarriage in staff

Advantages

a. moderately high potency

b. moderately low blood:gas partition coefficient
   → induction and recovery not prolonged
   moderately rapid changes in depth of anaesthesia

c. relatively non-irritant and bronchodilator
   → laryngospasm and bronchospasm uncommon

d. nonflammable & nonexplosive in combination with O_2

e. hypotensive effect sometimes desirable

f. uterine relaxation sometimes desirable

Disadvantages

a. only sleep is completely obtained
   → require additional analgesia, muscle relaxation, etc.

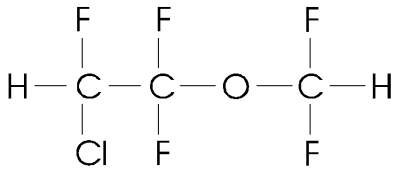
b. hypoxia/hypercapnia - respiratory depression

c. hypotension

d. transient arrhythmias - especially with adrenaline

e. post-operative hepatitis

ENFLURANE

Structure:	
Chemical name:	2-chloro-1,1,2-trifluoroethyl-difluoromethyl ether
Introduced:	1973 ?1972 (synthesised by Terrell 1963)
MAC:	1.68% 0.57% (70%-N_2O/O_2)
Partition Coefficient Bld-Gas: Oil-Gas: Fat-Bld:	 1.91 98
Saturated Vapour Pressure:	23% 175 mmHg (20°C)
Boiling Point:	56.5°C
Molecular Weight:	184.5 g

Cardiovascular

• decreases in BP, baroreceptor responses, preganglionic SNS activity, are approximately the same as for halothane at MAC equivalent doses
• as for halothane the circulatory responses are the best indicators of the depth of anaesthesia
• *in vitro*, enflurane produces a dose-dependent depression of myocardial contractility almost identical to, or ***slightly greater*** than halothane
• *in vivo*, however, enflurane does not decrease the HR and CO as much as halothane, the decrease in BP being partially due to decreased TPR, thus reducing LV afterload and helping maintain CO
• the decrease in myocardial work is paralleled by a reduction in O_2 consumption and there is ***no*** evidence of myocardial ischaemia
• both surgical stimulation and hypercarbia reverse the CO to preanaesthetic levels
• cardiovascular depressive effects are exaggerated by β-antagonists
• same precautions regarding β-blockers & CABG surgery apply c.f. halothane
• enflurane ***does not*** appear to significantly interfere with impulse generation, or conduction in the heart
• nor does it appear to sensitise the myocardium to adrenergic agonists

Respiration

NB: at 1 MAC, respiratory depression, hypercarbia, and inhibition of chemoreceptor responses are ***greater*** than produced by halothane, or isoflurane

→ assisted ventilation should nearly always be used,
but hyperventilation avoided due to the possibility of seizure activity

• enflurane actually decreases tidal volume the least of the three, however, unlike halothane or isoflurane there is no increase in respiratory rate,

→ ***minute volume*** is decreased the most by enflurane

• as with other anaesthetic gases, pulmonary oxygen exchange is impaired and supplemental O_2 is employed → $F_IO_2 \geq 30\%$ in the elderly
• as for halothane, enflurane causes ***bronchodilatation*** and inhibits bronchoconstriction

Nervous System

• a small proportion of subjects → tonic-clonic muscle activity
• investigation revealed characteristic EEG pattern with higher concentrations or ***hypocapnia***,

→ high voltage, 14-18 Hz pattern,
progressing to spike-dome complexes,
alternating with periods of electrical silence, or frank "seizure" activity

• this is not thought to be especially harmful but avoided in patients with known seizure foci, even though studies with epileptic patients failed to induce seizure activity
• most other CNS effects are similar to halothane,

a. CBF is increased when perfusion pressure is maintained
b. ICP follows changes in CBF and CPP
c. CSF formation is increased & CSF reabsorption decreased
→ ***increased*** CSF volume
d. decreased cerebral MRO_2

• in early systemic hypotension, CBF is maintained but then decreases as cerebral perfusion pressure continues to fall

Muscle

• enflurane causes ***greater*** muscle relaxation than halothane, and the enhancement of the effects of the competitive blockers is also greater
• this is due to both a CNS effect and an effect at the postjunctional membrane of the NMJ
• the later is not reversed by ***neostigmine***
• uterine muscle is relaxed, c.f. halothane this may enable foetal version, however is contraindicated at parturition

Renal System

• enflurane causes dose dependent reductions in,

a. glomerular filtration rate
b. renal blood flow, and
c. urine production

NB: same at equivalent MAC halothane & are readily reversible

• ***fluoride***, F^-, is a metabolite of enflurane
• values up to 20 µmol/l are frequently recorded
• however these rarely exceed the renal threshold for toxicity ~ 40-50 µmol/l
• low plasma F^- concentrations, (≤ 15 µmol/l), have been associated with a reduction of the maximal urine concentrating ability by up to 25% (W&W)
• the use of enflurane is probably safe with patients with renal disease, providing the depth & duration of anaesthesia are not prolonged

Liver and GIT

• intestinal and hepatic blood flow are reduced in proportion to the perfusion pressure, however delivery of oxygen is not compromised
• nausea and vomiting occur in ~ 3-15% of patients
• evidence of impaired hepatic function has been observed intraoperatively, however is readily reversed on cessation of anaesthesia
• ***hepatic necrosis*** has been reported with repeated administration of enflurane and those with previous sensitivities should receive another agent

Biotransformation

• 80% is exhaled as unchanged gas
• 2-5% is metabolised in the liver, by oxidative not reductive metabolism
• this low figure is due to,

i. the absence of ***bromine***
ii. the presence of the ***ether bond***
iii. the low oil:gas partition coefficient

NB: increased stability of the molecule & less available to the liver

• biotransformation may be increased by hepatic enzyme induction, however is not associated with an increase in renal toxicity, as occurs with methoxyflurane
• the major metabolites are,

i. difluoromethoxy-difluoroacetic acid
ii. F^- ion

NB: the ratio of free F^- released by the biotransformation of methoxyflurane, enflurane and isoflurane is **23:3:1** in rat microsomes

Advantages

a. moderately high potency

b. low blood:gas partition coefficient

→ rapid induction of and recovery from anaesthesia
rapid changes in depth of anaesthesia

c. relatively non-irritant and bronchodilator

→ laryngospasm and bronchospasm uncommon

d. nonflammable & nonexplosive in combination with O_2

e. muscle relaxation is often adequate for surgery

f. incidence of arrhythmias is less than halothane

g. uterine relaxation sometimes desirable

Disadvantages

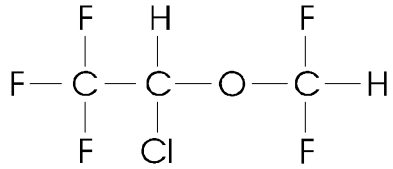
a. deep anaesthesia with enflurane

→ respiratory & circulatory depression
hypoxia/hypercapnia/hypotension

b. ***seizure activity*** may occur with high concentrations, or hypocarbia

c. uterine relaxation contraindicated at parturition

ISOFLURANE

Structure:	
Chemical name:	2,2,2-trifluoro-1-chloroethyl-difluoromethyl ether
Introduced:	1981
MAC:	1.15% 0.5% (70%-N_2O/O_2)
Partition Coefficient Bld-Gas: Oil-Gas: Fat-Bld:	 1.4 99
Saturated Vapour Pressure:	33% 250 mmHg (20°C)
Boiling Point:	48.5 °C
Molecular Weight:	184.5 g

Circulation

• produces a dose dependent reduction in BP, c.f. halothane & enflurane
• however, in contrast, CO is well maintained, the decrease in BP being due to ***vasodilatation*** and decreased TPR, especially in ***skin & muscle***
• direct myocardial depression has been demonstrated *in vitro*, however, this is not evident at normal gas tensions in man
• with spontaneous respiration, the ensuing hypercapnia and SNS stimulation result in increases in the HR & CO
• the cardiac and peripheral vascular effects are antagonised by β-blockade, and are thought to result in part from direct stimulation of β-receptors
• coronary blood flow is unaltered and myocardial MRO_2 is decreased in proportion to the reduction in myocardial work

→ this would suggest a wider margin of cardiovascular safety, c.f. H & E

• in theory, however, a ***subendocardial steal syndrome*** may result from dilation of coronary arterioles → diverting blood away from ischaemic regions in diseased hearts
• these circumstances are believed to exist in only ~ 23% of severe IHD patients (Eger 1989)

NB: to date, ischaemia during isoflurane anaesthesia has only been associated with significant degrees of ***hypotension***, therefore this contraindication requires further investigation (R.G. Merin, Adv. Anesthesia 1989)

• the HR is ***increased*** via reflex mechanisms but arrhythmias are uncommon
• isoflurane does not affect ventricular conduction and does not increase the excitability of ventricular myocardium
• ~ 3x the dosage of adrenaline may be employed for haemostasis

Respiration

• produces a dose dependent depression of respiration, approximately equivalent to that caused by halothane at 1 MAC $\rightarrow$ $P_{aCO2} \leq 50$ mmHg
• however, the depression of the normal responses to hypoxia & hypercapnia are depressed to a ***greater*** extent than halothane/enflurane
• spontaneous respiration $\rightarrow$ reduction of tidal volume but little change in respiratory rate
• produces similar reductions of pulmonary compliance and FRC
• this, with the inhibition of ***hypoxic pulmonary vasoconstriction*** $\rightarrow$ decreased efficiency of gas exchange seen with all three volatile agents
• preanaesthetic concentrations of isoflurane $\rightarrow$ airway reflex stimulation, with increased secretions and/or coughing and ***laryngospasm***
• therefore, intravenous induction is a greater priority
• at anaesthetic doses $\rightarrow$ ***bronchodilatation*** as do the other agents

Nervous System

• results in cerebral vasodilatation in addition to peripheral effects, thus,

a. CBF is increased, despite the decreased perfusion pressure
b. ICP is increased in proportion to CBF
c. CSF reabsorption is increased & CSF volume decreased
   $\rightarrow$ lessens the effects on ICP
d. cerebral vessels remain ***responsive*** to CO_2
   $\rightarrow$ ICP can be controlled by hyperventilation & hypocapnia

• EEG shows progressive changes with depth of anaesthesia,

i. 1 MAC - slow waves with increasing voltage
ii. 1.5 MAC - burst suppression
iii. 2 MAC - electrical silence

• unlike enflurane, isoflurane does not induce convulsive activity

Muscle

• reduces the response of skeletal muscle to sustained nerve stimulation, and enhances the blockade by depolarizing and non-depolarizing relaxants
• this results from actions on the CNS and NMJ, as for enflurane
• also, the increased blood flow due to peripheral vasodilatation enhances the delivery and removal of these agents to the muscle
• relaxation of uterine smooth muscle is the same as for halothane and enflurane

Kidney

• isoflurane produces dose dependent reductions in,

a. glomerular filtration rate
b. renal blood flow, and
c. urine production

NB: same at equivalent MAC as halothane & readily reversible

• the quantity of F^- ion released by degradation of isoflurane is small and there is no contraindication to its use in renal disease

Liver and GIT

• the incidence of nausea and vomiting is approximately the same as for other halogenated agents
• intestinal and hepatic blood flow are reduced in proportion to the perfusion pressure, however delivery of oxygen is not compromised
• there is minimal evidence of impaired hepatic function intraoperatively
• hepatic failure has not been reported with isoflurane (??)

Biotransformation

• only 0.2% of isoflurane is metabolised in the liver
• this figure is ~ 1% of the amount for halothane (15-50%), and 10% of that for enflurane (2-5%), and is due to,

i. the absence of ***bromine***
ii. the presence of the ether bond
iii. the low oil:gas partition coefficient
iv. the F_3C-C-O arrangement, increasing C-F bond strength

NB: increased stability of the molecule & less available to liver

• the major metabolites are,

i. trifluoroacetic acid
ii. F^- ion

• however, the quantities produced are insufficient to cause cell damage

Advantages

a. moderately high potency

b. low blood:gas partition coefficient

→ rapid induction of and recovery from anaesthesia
rapid changes in depth of anaesthesia

c. nonflammable & nonexplosive in combination with O_2

d. enhancement of muscle relaxation

e. incidence of arrhythmias is less than halothane

f. maintenance of CO and lack of myocardial depression

g. minimal biotransformation

h. ICP controllable via P_{aCO2}

Disadvantages

a. deep anaesthesia with isoflurane

→ respiratory & circulatory depression
hypoxia/hypercapnia/hypotension

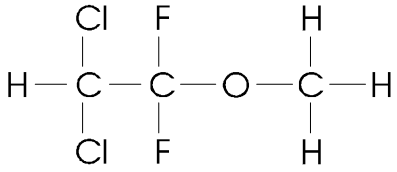
b. more pungent odour and initial respiratory ***irritation***

c. possible subendocardial steal syndrome with hypotension in IHD

d. uterine relaxation contraindicated at parturition

e. more expensive

METHOXYFLURANE

Structure:	
Chemical name:	2,2-dichloro-1,1-difluoroethyl-methyl ether
Introduced:	1960
MAC:	0.16%
Partition Coefficient Bld-Gas: Oil-Gas: Fat-Bld:	 12 970
Saturated Vapour Pressure:	3% 22.5 mmHg(20°C)
Boiling Point:	104.8 °C
Molecular Weight:	165 g

General Characteristics

• MF is the most potent of the inhalational agents
• because of its low vapour pressure and extreme solubility in rubber, as much as 30% of the agent may be lost in the anaesthetic circuit
• also, the high B:G coefficient further reduces the alveolar concentration early in induction

→ slow rise of F_A/F_I curve

• thus, despite the low MAC, even with high inducing concentrations of 2-3%, induction may take 20-30 minutes
• as for other agents, cardiovascular depression is the best guide to depth of anaesthesia
• the extreme solubility of this agent in adipose tissue results in an extended, though pain free, recovery period
• due to ***renal toxicity*** and the availability of safer and effective agents, clinical use today is limited

Cardiovascular

• decreases in HR, BP, baroreceptor responses, preganglionic SNS activity, are approximately the same c.f. halothane at MAC equivalent doses
• MF produces a dose-dependent depression of myocardial contractility, almost identical to halothane and, as for halothane, alters TPR little
• the reduction in BP being primarily the result of decreased cardiac ***contractility***
• the decrease in myocardial work is paralleled by a reduction in O_2 consumption and there is no evidence of myocardial ischaemia
• cardiovascular depressive effects are exaggerated by β-antagonists as for the other agents
• MF does interfere with impulse generation, conduction, and does sensitise the myocardium to adrenergic agonists, though, to a slightly lesser degree than halothane

→ same precautions with ***adrenaline***

Respiration

• respiratory depression, hypercarbia, and inhibition of chemoreceptor responses are approximately equal to those for halothane
• as with other anaesthetic gases, pulmonary oxygen exchange is impaired and supplemental O_2 is employed
• as for halothane, MF causes bronchodilatation and does not stimulate the respiratory tract, therefore premedication with atropine is not required

Nervous System

• most CNS effects are similar to halothane,

a. CBF increased when perfusion pressure maintained
b. ICP follows changes in CBF
c. decreased cerebral O_2 consumption
d. early in hypotension CBF maintained then decreases as pressure continues to fall

Muscle

• at deeper levels of anaesthesia, MF causes ***greater*** muscle relaxation than halothane, and the enhancement of the effects of the competitive blockers is also greater
• this is due to both a CNS effect and an effect at the postjunctional membrane of the NMJ
• the later is not reversed by neostigmine

NB: in contrast to the other volatile agents, MF ***does not*** relax uterine muscle, thus making it a useful agent for pain relief in the first stage of labour

Liver and GIT

• intestinal and hepatic blood flow are reduced in proportion to the perfusion pressure, however delivery of oxygen is not compromised
• impaired hepatic function is been observed intraoperatively, however is readily reversed on cessation of anaesthesia
• ***hepatic necrosis*** has been reported after administration of MF and probably relates to the metabolic products

Renal System

• MF causes dose dependent reductions in,

a. glomerular filtration rate
b. renal blood flow, and
c. urine production

NB: same at equivalent MAC value for halothane & readily reversible

• the major complication of MF anaesthesia is postoperative ***high output renal failure***, unresponsive to ADH
• ***fluoride***, F^- ion, is a major metabolite of MF
• patients receiving a dose equivalent to ^{3} ***2 MAC.hrs***, frequently have plasma concentrations above the renal threshold for toxicity (40-50 µmol/l), with resultant direct distal tubular damage

→ polyuria, dehydration, hypernatraemia, azotaemia

• in those who survive, recovery of renal function is usual, but may take up to 1 year

Biotransformation

• as much as ***50-70%*** of the absorbed dose is metabolised in the liver to,

i. F^- ion
ii. oxalic acid
iii. difluoromethoxyacetic acid
iv. dichloroacetic acid

• this high figure is due two factors,

i. despite the presence of the ether bond, the molecule is more susceptible to metabolism (ethyl C_1-F >> C_2-F)
ii. the extreme oil:gas partition coefficient

NB: decreased stability of the molecule & more is available to liver

• the peak serum F^- concentrations are found 2-4 days postoperative
• biotransformation may be increased by hepatic enzyme induction

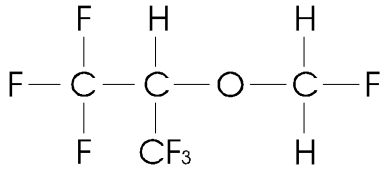
Advantages

a. provides profound analgesia
b. nonflammable & nonexplosive in combination with O_2
c. enhancement of muscle relaxation
d. doesn't relax uterine smooth muscle → analgesia in labour

Disadvantages

a. deep anaesthesia with MF
   → profound respiratory & circulatory depression
   hypoxia/hypercapnia/hypotension
b. renal toxicity has effectively removed it from general use
c. slow induction, changes of depth, and emergence from anaesthesia

SEVOFLURANE

Structure:	
Chemical name:	2,2,2-trifluoro-1-[trifluoromethyl]- ethyl-fluoromethyl-ether
Introduced:	Experimental
MAC:	1.71 ± 0.07% (Katoh 1987)
Partition Coefficient Bld-Gas: Oil-Gas: Fat-Bld:	 0.59 55
Saturated Vapour Pressure:	21% 160 mmHg (20°C)
Boiling Point:	58.5°C
Molecular Weight:	200 g

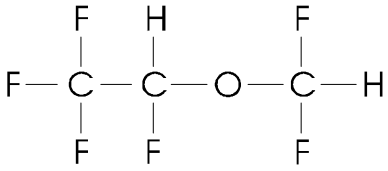
General Characteristics

• the clinically derived MAC is below that predicted by O:G partition coefficient → 2.6%
• volatile, nonflammable, halogenated ether which has the second lowest B:G solubility of the volatile inhalational agents
• it has a pleasant odour enabling very rapid induction & emergence

→ highly suitable for paediatric anaesthesia

• biotransformation is similar to that for enflurane, with subnephrotoxic levels of F^- being reached
• no other signs of viscerotoxicity have been found in animal models
• depresses the CVS but to a lesser degree than halothane and does not sensitise the myocardium to catecholamines
• no signs of increased CNS activity have yet been found
• unstable in ***soda-lime***, however, metabolites are apparently non-toxic
• Miller states that it was withdrawn from clinical trials in 1980, possibly due to some reports of renal toxicity

DESFLURANE

Structure:	
Chemical name:	2,2,2-trifluoro-1-fluoroethyl-difluoromethyl ether
Introduced:	Experimental
MAC:	6
Partition Coefficient Bld-Gas: Oil-Gas: Fat-Bld:	 0.42 ?
Saturated Vapour Pressure:	87% 663 mmHg (20°C)
Boiling Point:	23.5°C
Critical Temperature:	?
Molecular Weight:	168 g

General Characteristics

• the low solubility plus high vapour pressure:MAC ratio enable very rapid gaseous induction, similar figure c.f. cyclopropane
• desflurane is less pungent than isoflurane or enflurane, but more than sevoflurane or halothane
• even so, the very rapid induction & emergence

→ highly suitable for paediatric anaesthesia

• minimal metabolism and free F^- production less than isoflurane
• cost is likely to be the only negative factor preventing its widespread use
• plus the requirement for pressurised delivery systems due to the low boiling point
• one report of raised ICP unresponsive to hyperventilation, therefore may be contraindicated in neuroanaesthesia

NB: Muzzi et al. Anaesthesiol. 1992

→ ↑ ICP with supratentorial tumours > isoflurane

Summary of Volatile Agent Effects			
System	Halothane	Enflurane	Isoflurane
Cardiovascular			
• heart rate	--	+/-	+/-
• blood pressure	-	-	-
• myocardial contractility	--(-)	---	-
• stroke volume	---	---	-
• TPR	0(-)	--	---
• cardiac output	-	--	0(-)
• LVED pressure	++	++	0(+)
• coronary blood flow	--	--	(-)
• coronary resistance	+/-	-/+	--(-)
• conduction (AV & LV)	---	(-)	(-)
• myocardial excitability	+++	+	0(+)
Central Nervous System			
• cerebral blood flow	++	++	+
• vascular resistance	--	--	(-)
• oxygen consumption	--	--	-(-)
• cerebrospinal fluid			
◦ formation	+	+	0
◦ reabsorption	+	-	+
◦ volume	0	++	-
• intracranial pressure	++	+++	+/-
• excitability	0	+++	(+)
Respiratory			
• minute ventilation	-	---	-
• tidal volume	--	-	--
• respiratory rate	+	-	+
• bronchial irritation	+	++	+++
• bronchial tone	-	-	-
Reflexes			
• baroreceptor	--	(-)	-
• chemoreceptor			
◦ central	-	-(-)	--
◦ peripheral	-	--	--(-)

NITROUS OXIDE

Structure:	$N \equiv N = O$	
Chemical name:	dinitrogen monoxide	
Introduced:	1844	
MAC:	105%	
Partition Coefficient Bld-Gas: Oil-Gas:	 0.47 1.4	
Critical Temperature:	**36.5°C**	
Boiling Point:	-88°C	
Liquifying Pressure (36.5°C):	74 bar	? 72 bar
Vapour Pressure (20°C):	52 bar	39,000 mmHg
Normal Cylinder Pressure:	**52 bar**	
Molecular Weight:	44 g	

General Characteristics

- N_2O is a colourless gas, without appreciable odour or taste
- first synthesised by ***Priestly*** in 1772
- first used in anaesthetic practice by ***Cotton & Wells*** in 1844
- marketed in steel cylinders as a liquid under pressure in equilibrium with the gas phase at normal room temperature
- the normal ***filling ratio* = 0.65**
- heat is required to vaporise the liquid, latent heat of vaporisation
- if this is rapid the cylinder becomes cold, lowering the vapour pressure of the cylinder
- the gas is neither flammable, nor explosive, but will support combustion of flammable agents

▪ *Chemical Preparation*

- prepared commercially by heating ***ammonium nitrate*** between 245-270 °C

$$NH_4NO_3 \xrightarrow{\textit{Heat}} N_2O + 2H_2O$$

- contamination with the higher oxides of nitrogen, ***nitrogen dioxide*** or ***nitric oxide***, may lead to,
  a. laryngospasm
  b. cyanosis due to methaemoglobinaemia
  c. chemical pneumonitis and respiratory failure

Pharmacokinetics

• nitrous oxide is a ***potent analgesic*** agent but a weak anaesthetic agent, producing surgical anaesthesia predictably only under hyperbaric conditions
• the rate of approach of alveolar to inspired concentration is rapid due to the low solubility in blood
• the rate of uptake, after inhalation of a 80%-N_2O/20%-O_2 mixture,

a. at 1 min ~ 1000 ml/min
b. at 5 min ~ 500 ml/min
c. at 90 min ~ 100 ml/min

• the time taken to reach 90% arterial saturation is about 20 min
• this large uptake of gas, and rapid egress on emergence, results in,

a. the concentration effect
b. the second gas effect
c. diffusion hypoxia

• although N_2O has a "low" blood solubility c.f. other anaesthetic agents, it is considerably more soluble than nitrogen (0.014) **~ 34 times**
• therefore, any closed, gas-filled cavity will expand during nitrous oxide anaesthesia as nitrogen is exchanges for N_2O, e.g.,

a. pneumothorax
b. occluded middle ear
c. pneumopericardium
d. closed loop intestinal obstruction
e. renal or lung cysts
f. pneumocranium

• the main value of nitrous oxide in anaesthesia is as an adjuvant to the inhalational agents
• with inhalation of 70%-N_2O / 30%-O_2, the MAC values are reduced ~ 35-45% as follows,

a. halothane 0.74% $\rightarrow$ 0.29%
b. enflurane 1.68% $\rightarrow$ 0.58%
c. isoflurane 1.15% $\rightarrow$ 0.50%

NB: smaller doses of the volatile agents, with N_2O, result in equal anaesthesia but less cardio-respiratory depression

Central Nervous System

- N_2O depresses the CNS and produces analgesia
- N_2O increases cerebral blood flow and raises ICP
- however these remain responsive to changes in the P_{aCO2} and are less effected than with the volatile agents
- when used with barbiturate induction + droperidol/fentanyl + relaxant,

  → good anaesthesia and a moderate ***fall*** in ICP

Cardiovascular System

- effects depend upon whether N_2O is administered alone, with a volatile agent, or with narcotics,

a. N_2O alone
   - small, direct myocardial depressant effect
   - CO, contractility & HR reduced
   - TPR increases, therefore no change in BP
   - small increase in circulating NA

b. N_2O + ***volatile***
   - circulating NA increases
   - CO, HR, TPR & BP all > volatile alone
   - SNS activation: Halothane > Isoflurane ~ Enflurane
   - increases the ***arrhythmogenic*** potential of all agents
   - less volatile agent required, therefore less cardiorespiratory depression

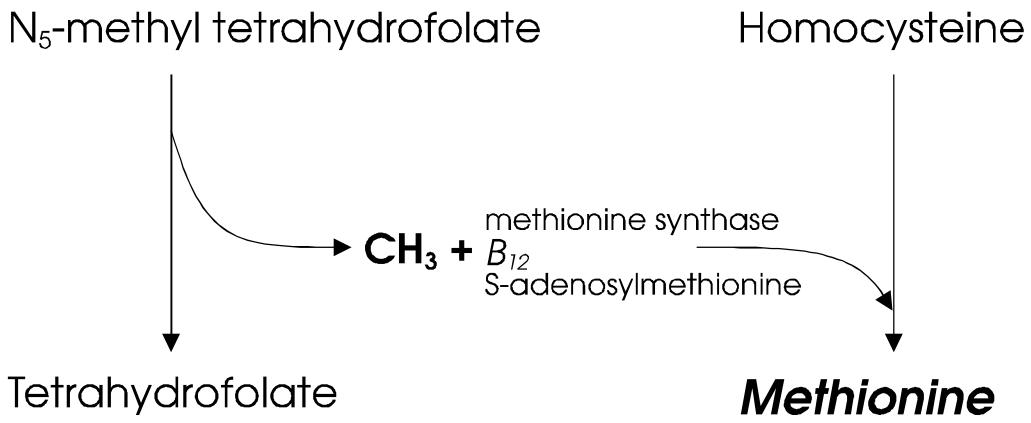
c. N_2O + ***narcotic***
   - generally causes only further circulatory depression
   - TPR may increase but this further reduces CO
   - with high dose fentanyl and poor LV function, myocardial depression may be clinically significant

Respiratory System

- effects on respiration are generally small
- there is no change in the respiratory response to CO_2
- there is a decrease in ***hypoxic drive*** when 50% N_2O is inspired
- there is no change in bronchomotor tone

Interaction with Vitamin B_{12}

• B_{12} is a bound coenzyme of ***methionine synthase***, having a tetrapyrrole ring and a central cobalt atom
• N_2O ***oxidizes*** the cobalt from Co^{+} to Co^{++}, which can no longer function as a methyl carrier
• oxidation is ***irreversible*** and new enzyme has to be synthesised → effects last up to 3 days



NB: blockade of this reaction appears to be the sole metabolic action of N_2O, with a subsequent reduction of the two products,

i. tetrahydrofolate
ii. methionine

• ***methionine*** is a dietary constituent, however daily requirements are ~ 2 times the average intake
• in addition to its role in protein synthesis, methionine acts as a precursor to ***S-adenosylmethionine*** (SAM), which is a direct methyl donator in a number of important reactions,

a. noradrenaline → adrenaline
b. synthesis of arachidonic acid
c. myelination of nerves
? decreased SAM → subacute combined degeneration of the cord
d. SAM → active formate, + THF → ***10-formyl-THF***

• the product 10-formyl-THF is a precursor to 5,10-methylene-THF which is essential for the production of the essential DNA base ***deoxythymidine***
• after administration of N_2O the first detectable changes are a reduction in methionine synthase activity, followed soon after by an interference with DNA synthesis
• the later is manifest by an abnormal ***deoxyuridine suppression test***

• following very prolonged administration, (≥ 4 days), ***agranulocytosis*** is an almost universal result

NB: "interference with ***thymidine synthesis*** is to be expected in man after 12 hrs of exposure to N_2O, but may appear within 2h or even less" Nunn (BJA 1987)

• subsequent recommendations (Nunn),

a. $N_2O > 24h$ → absolute contraindication

b. $N_2O \sim 24h$ → reasonable for healthy patient
bone marrow will be ***megaloblastic***
abnormal dU-suppression test

c. $N_2O \geq 2h$ → hepatic ***methionine synthase*** will be depressed
effects on DNA synthesis unpredictable

d. $N_2O \leq 0.5h$ → no measurable effect
cumulative if interval < 3 days

• replacement R_X with ***methionine*** reduced the occurrence of neurological sequelae in experimental monkeys
• administration providing SAM for methyl transfer
• this should theoretically also apply to man

• replacement R_X with ***folinic acid***, (5-formyl-THF), cannot restore methionine levels, or its products (SAM), but it can restore ***deoxythymidine synthesis***
• there is irrefutable evidence that N_2O is a mild ***teratogen*** and this is undoubtedly due to its effects on DNA synthesis
• therefore, the use of N_2O in pregnancy during the period of ***organogenesis*** is inadvisable
• if necessary, cover with folinic acid may offer some protection

NB: the possibility of N_2O abuse should be considered in any person with access to the gas who presents with symptoms & signs resembling ***subacute combined degeneration*** of the cord - especially dentists!!

Other Organ Systems

• skeletal muscle does not relax in the presence of 80% N_2O, and muscle blood flow is unaltered
• unlike the halogenated GA's, N_2O is most unlikely to contribute to malignant hyperpyrexia
• the liver, kidneys, and GIT show no marked effects in response to N_2O, and there is no evidence of toxicity
• N & V occur in ~ 15% of patients postoperative

Biotransformation

- rapidly and predominantly eliminated unchanged through the lungs
- significant biotransformation is unable to be assessed

Advantages

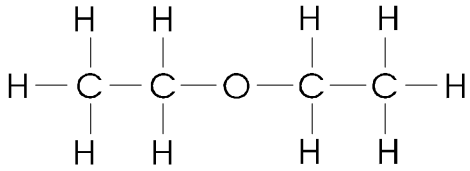
a. nonflammable & nonexplosive
b. non-irritant
c. potent analgesic
d. very rapid onset, changes in depth and recovery
e. little or no toxicity during normal applications

Disadvantages

a. weak anaesthetic agent
b. no augmentation of muscle relaxation
c. diffusion hypoxia on recovery
d. expansion of closed internal air-spaces
e. depressed methionine synthase activity

→ megaloblastic marrow changes
demyelination of the cord in long term abusers

DIETHYL ETHER

Structure:	
Chemical name:	di-ethyl ether
Introduced:	1846
MAC:	1.92
Partition Coefficient Bld-Gas: Fat-Bld:	 12 49
Saturated Vapour Pressure:	58% 442 mmHg (20°C)
Boiling Point:	36.5 °C
Molecular Weight:	74 g
Flammable Range	2-36.5% Air 2-82% O_2

General Properties

- first prepared by V. Cordus in 1540 by condensation with ***sulphuric acid***
- used for tooth extraction by W.E. Clarke in 1842
- ? first used by Crawford Long of Georgia
- first public demonstration by W. Morton in 1846 in Boston

- highly volatile and poor stability, therefore avoid light, heat, air
- compatible with soda lime circuit
- excellent analgesic $\rightarrow$ stages/planes of anaesthesia (Guedel - see over)
- stimulates respiration, therefore less danger of hypoxia
- stimulates respiratory secretions, therefore need atropine
- increases SNS activity but low arrhythmic potential
- causes uterine relaxation
- may cause hyperglycaemia
- postoperative vomiting a major problem
- ***chemical preparation*** by condensation of ethyl alcohol,

$$2\ C_2H_5\text{-}OH \longrightarrow C_2H_5\text{-}O\text{-}C_2H_5 + H_2O$$

Stages of Anaesthesia - Guedel

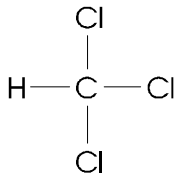
- ***Stage Of Analgesia***
  - from the beginning of ***induction*** to the ***loss of consciousness***

- ***Stage Of Delerium***
  - from the ***loss of consciousness*** to the beginning of ***surgical anaesthesia***
  - excitement ± involuntary movement may be minimal or marked
  - breathing is irregular
  - skeletal muscle tone increases
  - increases in BP & HR may be marked
  - * the duration of this stage should be minimised

- ***Stage Of Surgical Anaesthesia***
  - from the beginning of ***surgical anaesthesia*** to the cessation of ***respiration***
  - divided into four planes according to the depth of anaesthesia
  - differentiation is by assessment of
    i. respiration
    ii. eyeball movements
    iii. pupillary size
    iv. reflex responses

- ***Stage Of Medullary Depression***
  - from the weakened respiration of Plane 4, Stage 3 to circulatory failure

CHLOROFORM

Structure:	
Chemical name:	trichloromethane
Introduced:	1847
MAC:	0.72%
Boiling Point:	61 °C
Molecular Weight:	119 g

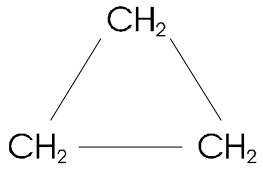
General Properties

- anaesthetic action discovered by P. Flourens in France 1847
- first employed by Simpson, in Scotland 1847
- nonflammable
- compatible with soda lime circuit
- may contain impurities → phosgene, chlorine, carbon tetrachloride
- stabilised by 0.6 - 1% ethyl alcohol
- light anaesthesia in the presence of adrenaline → VF
- increases SNS activity
- depresses hepatic function and in large doses is hepatotoxic
- may also be nephrotoxic

Manufacture

- acetone with chlorine and lime; or, hydrogenation of carbon tetrachloride
- in the presence of iron

CYCLOPROPANE

Structure:	
Chemical name:	cyclopropane
Introduced:	1844
MAC:	9.2%
Critical Temperature:	124.7°C
Boiling Point	-32.9°C
Saturated Vapour Pressure:	6.3 bar ~ 90 psi (20°C)
Normal Cylinder Pressure:	? bar
Flammable Range	2.4- 10.3% Air ? - 60% O_2
Molecular Weight:	42 g

General Properties

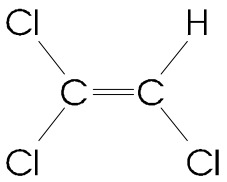
- first prepared by Freud, in Germany in 1881
- first used for anaesthesia by R.M. Waters, in U.S.A.
- must use in ***closed circuit*** to minimize cost and reduce danger of explosion
- incompatible for use with nitrous oxide, as supports combustion
- very rapid induction
- SNS stimulant $\rightarrow$ "cyclopropane shock"
- respiratory depressant
- ***arrhythmogenic***, therefore must avoid adrenaline
- good muscle relaxant

Manufacture

- found as a natural gas
- produced from dihalide propane,

$$CH_2Cl\text{-}CH_2\text{-}CH_2Cl + Zn^{++} \longrightarrow \text{cyclic } -CH_2\text{-}CH_2\text{-}CH_2- + ZnCl_2$$

TRICHLORETHYLENE

Structure:	
Chemical name:	trichlorethylene
Introduced:	1934
MAC:	0.17
Partition Coefficient Bld-Gas: Oil-Gas:	 9.15 ?
Saturated Vapour Pressure:	8.5% 64.5 mmHg(20°C)
Boiling Point:	86.7°C
Molecular Weight:	131 g

General Properties

- first manufactured by Fischer in Germany in 1864
- first used clinically by Jackson in U.S.A. in 1934

- nonflammable
- unstable in soda lime circuit → ***dichloracetylene***
- this causes cranial nerve palsies, esp. V & VII
- stabilised with ***thymol 0.01%***
- potent analgesic
- increases vagal tone but BP stable
- arrhythmogenic, therefore problems with adrenaline
- tendency to cause tachypnoea
- approximately 25% metabolised
- causes significant nausea and vomiting

Manufacture

- from acetylene and chlorine → $CHCl=CCl_2$